Osteoporosis drug treatment: duration and management after discontinuation. A position statement from the SVGO/ASCO

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Osteoporosis drug treatment: duration and management after discontinuation. A position statement from the Swiss Association against Osteoporosis (SVGO/ASCO)

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Summary

Antiosteoporotic drugs are recommended in patients with fragility fractures and in patients considered to be at high fracture risk on the basis of clinical risk factors and/or low bone mineral density. As first-line treatment most patients are started with an antiresorptive treatment, i.e. drugs that inhibit osteoclast development and/or function (bisphosphonates, denosumab, oestrogens or selective oestrogen receptor modulators). In the balance between benefits and risks of antiresorptive treatment, uncertainties remain regarding the optimal treatment duration and the management of patients after drug discontinuation. Based on the available evidence, this position statement will focus on the long-term management of osteoporosis therapy, formulating decision criteria for clinical practice.

Key words: *osteoporosis, fractures, treatment, bisphosphonates, denosumab*

Introduction

Osteoporosis is a chronic metabolic disease characterised by a progressive loss of bone mass and microarchitectural deterioration, ultimately resulting in an increased risk of fragility fractures. During recent decades remarkable advances have been made in the diagnosis and treatment of osteoporosis. Specifically, and based on the understanding of the pathogenesis of osteoporosis, new treatment options including antiresorptive and anabolic treatment modalities have been developed and introduced into clinical routine.

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In treatment guidelines, antiosteoporotic drugs are recommended for patients with vertebral or nonvertebral low-trauma fractures and for patients who present with a high fracture risk based on clinical risk factors and/or low bone mineral density (BMD) [1]. As first-line treatment, most patients are started with an antiresorptive treatment, i.e., a drug that inhibit osteoclast development and/or function (bisphosphonates, denosumab or selective oestrogen receptor modulators [SERMs]). In younger women up to the age of 60 years or up to 10 years after menopause, menopausal hormone therapy is recommended [2]. Its fracture preventive effect has been shown to be significant in postmenopausal women, even those without increased fracture risk [3]. In this age group, no long-term data are available for the nonhormonal antiresorptive alternatives [2]. In the balance between benefits and risks of antiresorptive treatment, uncertainties remain regarding the optimal treatment duration and the management of patients after drug discontinuation.

Alternatively, teriparatide, a recombinant human parathyroid hormone analogue, increases the formation of new bone substance by virtue of its stimulating effects on osteoblasts [4]. In Switzerland, teriparatide is approved for second-line treatment in patients with progressive osteoporosis or glucocorticoid-induced osteoporosis. However, as a result of its pronounced anabolic effect, particularly at cancellous bone sites (such as the vertebrae), its use as a first-line treatment option is increasingly recommended in patients at high fracture risk [5].

Based on the available evidence, this position statement will focus on the long-term management of osteoporosis therapy, formulating decision criteria for clinical practice.

Treatment modalities and their mode of action

Bisphosphonates are pyrophosphate analogues that act mainly by inhibiting osteoclast-mediated bone resorption. They are characterised by a high affinity with bone and a long half-life within the skeleton [6, 7]. The identification of the receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG) as central regulators of bone metabolism has resulted in the development of *denosumab*, a human monoclonal antibody against RANKL. An understanding of its mode of action, as compared to that of bisphosphonates, is essential to appreciate the differences in their use. Bisphosphonates accumulate on mineralised bone surface and are internalised by mature osteoclasts. Because of their long lasting retention on bone surface (particularly so for alendronate and zoledronate), bisphosphonates have a unique residual treatment effect on bone resorption even after treatment discontinuation. In contrast, circulating denosumab inhibits the maturation of osteoclasts by binding to and inhibiting RANKL. Thereby the effect of denosumab is limited to the period of drug exposure, i.e., the duration of treatment [8]. Importantly, discontinuation of denosumab is associated with a significant bone turnover rebound and a rapid loss of bone mass [9, 10], a phenomenon that has not been observed after discontinuation of bisphosphonates [7].

The effect of *menopausal hormone therapy* on bone metabolism ends with the cessation of oestrogen administration. However, a long lasting decrease of fracture risk has been confirmed for all major fractures up to 16 years after discontinuation of hormone therapy [3, 11–13]. To reach this protective effect, the number needed to treat (NNT) is 7 [11].There is no reason to place mandatory limits on the duration of menopausal hormone therapy. Data from the WHI trial and other studies support safe use for at least 5 years in healthy women starting treatment before the age of 60 [2].

The mode of action of *teriparatide* is related to its ability to stimulate processes associated with bone formation, which are then coupled to processes associated with bone resorption, leading to an overall increase in bone remodelling, but with a positive balance towards bone formation [14]. The bone formation induced by teriparatide not only increases bone mass but also improves the microarchitecture of the skeleton, primarily the trabecular and cortical thickness, thereby leading to improved strength and increased mechanical resistance. However, teriparatide also increases intracortical bone remodelling, leading to some porosity, which may partly explain the transient decline of BMD at predominantly cortical bone sites (such as the distal radius and femoral neck). As for many antiresorptive agents (except for bisphosphonates), effects of teriparatide on bone turnover are transient and limited to the time of exposure. Hence, sequential therapy with antiresorptive drugs is needed to improve secondary mineralisation and maintain bone mass [15, 16].

Duration of treatment

Benefits and safety during long-term-treatment

There is consensus that patients with high fracture risk should receive pharmacological treatment to prevent fragility fractures. The decision for how long to treat with antiresorptive drugs is largely dependent on their long-term efficacy and safety.

A network meta-analysis of several pharmacological agents available for the prevention of fragility fractures found strong evidence to support the efficacy of bisphosphonates (alendronate, risedronate, zoledronate), denosumab and teriparatide in reducing the relative risk of vertebral fractures by 40–70% and nonvertebral fractures by 20–40% [17]. For antiresorptives, this translates into a NNT of 15–25 to prevent one vertebral fracture over 3 years of treatment. However, one has to bear in mind that the NNT depends largely on the fracture incidence in the study population, with a lower NNT in high risk patients.

Data on fracture risk reduction during long-term treatment are mainly available for antiresorptive drugs. Indeed, the use of teriparatide as an anabolic drug is limited to 24 months duration. Among antiresorptives, the results of extension studies with alendronate, risedronate and zoledronate have been analysed. Postmenopausal women treated with alendronate for 4 to 5 years in the Fracture Intervention Trial (FIT) were randomised to continue with alendronate for 5 years or switched to placebo (FLEX Study) [18]. Postmenopausal women who had already received three annual intravenous infusions of zoledronate (Horizon Study) were randomised to either continue with yearly zoledronate or switch to placebo for another 3 years (Horizon Study Extension) [19]. The results of the 10 years of therapy with alendronate and the 6 years with zoledronate were a slight reduction in clinical and/or morphometric vertebral fractures as compared with stopping alendronate after 5 years or zoledronate after 3 years, since in the latter case the incidence of vertebral fractures increased again after discontinuation of therapy. In the FLEX study, continuation of alendronate for 10 years instead of stopping after 5 years decreased nonvertebral fractures only in women whose femoral neck T-score was -2.5 standard deviations (SD) or less at the time of discontinuation. However, non-spine fracture incidence was similar in those who continued 10 years alendronate or 6 years zoledronate, compared with those who stopped active treatment during the extension studies [20]. Notably, these extension studies were not primarily designed for fracture outcomes, but to look at BMD changes upon continuation or discontinuation of therapy (BMD progressively declining upon treatment cessation), and were also limited in the number of patients who were enrolled long-term.

The antifracture efficacy data on long-term treatment with denosumab, up to 10 years, are reported from the Extension study of the FREEDOM trial. In the open-label Extension study, 4550 postmenopausal women with osteoporosis who previously received either denosumab (long-term treatment group) or placebo (crossover group) were assigned to receive denosumab for another 7 years. After significant reduction of vertebral and nonvertebral fractures in the denosumab-treated group as compared with placebo during the FREEDOM study (first 3 years), the yearly incidence of new vertebral fractures remained low, whereas nonvertebral fractures further significantly decreased in year 4 [21] and then remained stable (approximately 1.5% per year for both vertebral and nonvertebral fractures in years 4 to 10 of continuous therapy) [22].

In general, antiresorptive drugs have a good safety profile. The side-effects vary between drugs, but many are as-

sociated with gastrointestinal effects after intake of oral bisphosphonates or influenza-like symptoms after intravenous bisphosphonate application (e.g., zoledronic acid). Nevertheless, for bisphosphonates and denosumab rare but serious adverse events have been reported, including osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) [23]. ONJ is associated with oncology-dose parenteral antiresorptive therapy with bisphosphonates and denosumab. The incidence of ONJ is greatest in the oncology patient population (1–15%), where high doses of these medications are used at frequent intervals. In the osteoporosis patient population. However, the incidence of ONJ is estimated to be 0.01 to 0.025%, and increases with treatment duration. The incidence is marginally higher than the incidence in the general population (<0.001%) [24]. Atypical femoral fractures located in the subtrochanteric region and diaphysis of the femur have been reported in patients taking bisphosphonates or denosumab, but are also observed in individuals without specific bone medication. The absolute risk of AFFs in patients on bisphosphonates is extremely low, ranging from 3.2 to 50 cases per 100 000 person-years [25]. However, long-term use for more than 5 years may be associated with higher risk [26]. When bisphosphonates are stopped, risk of an AFF rapidly declines. It is important to note that in treated women the absolute risk for atypical fractures is up to 100-fold less than the risk for hip fracture among untreated postmenopausal women with high fracture risk [27].

Hence, for the efficacy of bisphosphonates and denosumab to reduce hip fractures, the benefit-risk ratio of these drugs remains favourable, particularly in patients at high fracture risk.

For the decision about antiresorptive treatment duration in an individual patient, reassessment of fracture risk is essential. A patient is considered to remain at high risk of fracture if they (a) experienced hip, spine or multiple osteoporotic fractures within 5 years before and/or during therapy, (b) remain on continuous high fracture risk based on clinical judgment or comorbidities, or (c) present with persistent low BMD. Subgroup analyses of the extension studies mentioned above indicate that patients whose femoral neck (or total hip) BMD T-score remains below -2.5 SD after 5 years of therapy benefit most from continuing antiresorptive therapy [21, 28–30]. As age and falls are major risk factors for fracture, a T-score threshold of -2.0 SD for continuation of antiresorptive therapy seems reasonable in older women (>65 years) and/or in frequent fallers.

Management after discontinuation of therapy

As a rule, the effects of any drug vanish upon treatment discontinuation, so that if the disease is chronic, symptoms and complications will recur (e.g., high blood pressure and risk of stroke upon cessation of antihypertensive medicines, hyperglycaemia and related complications upon cessation of antidiabetic drugs). The same is true for most osteoporosis drugs, including oestrogens, SERMs, denosumab and teriparatide. Bisphosphonates, because of their high affinity for bone, remain in the skeleton even after the drug is discontinued, which explains the slower and/or retarded offset of effects, with a slight decrease in bone mineral density and increase in biochemical markers of bone turnover, but to levels which can remain below pretreatment levels for months to years [18, 19].

On the other hand, discontinuation of denosumab has been associated with an increase of bone turnover markers to above-baseline levels (rebound); these return to baseline levels within 2 years of treatment cessation. In parallel, BMD decreases to baseline levels within 1 to 2 years, regardless of the duration of previous therapy [10]. Recently, after a few clinical cases of vertebral fractures were reported upon cessation of denosumab therapy [31, 32], a preliminary observation in more than 1000 subjects from the FREEDOM study and its extension who discontinued denosumab or placebo, indicated that vertebral fracture incidence indeed increased nearly 4-fold within a year after denosumab was stopped [33]. However, the absolute incidence of vertebral fracture remained comparable to that observed in subjects who discontinued placebo. Nevertheless, among subjects who sustained a new vertebral fracture after discontinuing denosumab, the incidence of multiple new vertebral fractures tended to be higher than in subjects who discontinued placebo [33]. Indirect comparison of the FREEDOM results with those of the bisphosphonates extension studies (above) which showed that the risk of vertebral fractures nearly doubles upon cessation of bisphosphonate therapy, suggests that more patients may sustain severe vertebral fractures when stopping denosumab, which is consistent with the quick reversibility of its antiresorptive effects. These observations led the medical authorities in Switzerland, in agreement with the company (Amgen) to adapt the drug label in order to warn prescribers against the sudden interruption of denosumab and the need to consolidate therapy with at least one year of a non-reversible antiresorptive. Currently identified risk factors for vertebral fractures after discontinuation of denosumab include prevalent fractures, BMD loss and longer duration off therapy [32, 34]. In this context, it should be noted that some data suggest that the rebound in bone resorption and BMD can be avoided in patients previously treated with bisphosphonates, probably due to their persistence in bone tissue [35, 36].

Practical consequences

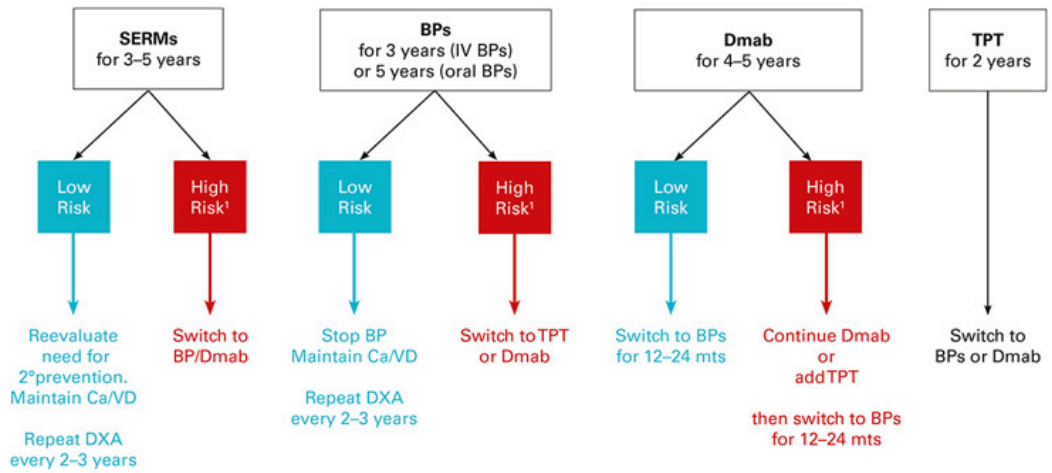
On the basis of the above mentioned data on the efficacy and safety of antiresorptive drugs, we propose an approach to aid decisions about the management of patients with osteoporosis on long-term therapy (fig. 1). Because the extension trials that suggested long-term anti-fracture efficacy based on continuation vs discontinuation of therapy were conducted exclusively in postmenopausal women, the suggested approach is restricted to the management of women with postmenopausal osteoporosis. Nevertheless, similar approaches in male osteoporosis seem reasonable. Furthermore, the suggestions on long-term osteoporosis treatment modalities described below are not evidence based, but represent interpretation of the current data. Further studies are needed to elucidate antifracture efficacies of proposed sequential treatment algorithms.

1. Regular *reassessment of fracture risk* for decision of treatment duration is essential. A patient is considered to remain at high risk of fracture if any of the conditions below is present:

hip, spine or multiple osteoporotic fractures within 5 years before and/or during therapy;
high fracture risk score at baseline according to FRAX® and/or continuously high fracture risk based on clinical judgment or comorbidities (e.g., continuous use of aromatase inhibitors for breast cancer, diabetes, frailty);
persistent low BMD: on the basis of the above-mentioned extension trials (FLEX study, HORIZON- and FREEDOM-Extension studies), patients with a T-score persistently lower than -2.5 SD at the femoral neck (or <-2.0 SD in older patients and/or frequent fallers) benefit the most from continuing therapy.

2. For postmenopausal women who have been on *oral or intravenous bisphosphonate therapy* for 3 years (intravenous) to 5 years (oral), reassessment of individual fracture risk is mandatory. In women at high risk (see above), treatment should preferentially be switched to denosumab, as comparison studies have shown superiority of denosumab over bisphosphonates in treatment-related changes in BMD [37]. For women with an incident vertebral fracture bone-anabolic treatment with teriparatide for 24 months is advised. Alternatively, continuation of treatment for up to 10 years (oral bisphosphonates) or 6 years (intravenous bisphosphonates) may be considered, depending on the risk (increased risk of ONJ and AFF) and the benefit (fracture risk reduction). In patients with low-to-moderate fracture risk, a drug holiday is suggested with clinical, biochemical and densitometric reassessment every 2 to 3 years.
3. For postmenopausal women who have been on *treatment with SERMs* for 3 to 5 years and are considered at high fracture risk (see above) switching treatment to BPs or denosumab should be considered.
4. For postmenopausal women who have been on *denosumab therapy* for at least 3 to 5 years, reassessment of individual fracture risk is suggested. In women at high risk (see above), continuation of treatment for up to 10 years should be considered. Specifically, continuation of treatment is considered in women on an aromatase inhibitor. In the case of very high fracture risk (incident new vertebral fractures during denosumab therapy), combination therapy, with teriparatide for 24 months followed by antiresorptive therapy, should be considered on the basis of the favourable effects of combination therapy on BMD, although evidence for fracture risk reduction is lacking [38, 39].
5. In women with a favourable treatment response in which *denosumab therapy discontinuation* is considered (low fracture risk, BMD increase into age-adjusted range, cessation of aromatase inhibition), sequential treatment with non-reversible antiresorptives (bisphosphonates, or SERMs in cases of bisphosphonate intolerance) is mandatory, particularly in older women with prevalent vertebral fractures and in women without previous long-term therapy with one of the more potent bisphosphonates (alendronate, zoledronate). Sequential therapy may be guided by the rebound in bone turnover markers, particularly in patients with prior bisphosphonate therapy [35, 39]. Treatment with non-reversible antiresorptives may be needed for up to 12 to 24 months.
6. In patients suffering *vertebral fractures after discontinuation of denosumab,* percutaneous vertebral cement augmentation should be used with caution as vertebroplasty has been associated with a high number of new vertebral fractures in these circumstances [31]. Pharmacological treatment should be restarted, either with denosumab (eventually in combination with teriparatide) or zoledronate.
7. The anabolic effects of *teriparatide* on bone are transient and limited to the time of exposure. Sequential therapy with antiresorptive drugs (bisphosphonates, denosumab) drugs is mandatory to maintain bone mass and improve secondary mineralisation.

Figure 1: Approach to the management of postmenopausal women on anti-osteoporotic therapy.[1] High risk defined as (a) hip, spine or multiple fractures before or during therapy; (b) femoral neck T-score <-2.5 SD if age <65 years, <-2.0 SD if age >65 years and/or frequent falls; (c) continuing hormone ablative therapy (e.g., aromatase inhibition, androgen deprivation therapy); (d) secondary osteoporosis, continuing glucocorticoid therapy.BP =bisphosphonate; Ca/VD = calcium and vitamin D supplementation; Dmab, denosumab; DXA = densitometry; SERM = selective oestrogen receptor modulator; TPT = teriparatide



8. When considering the duration of and options for osteoporosis treatment, the potential contributions of poor compliance or adherence to therapy, inadequate vitamin D status, high fall risk, or new risk factors should be considered. Current guidelines recommend that treatment of any osteoporotic drug should always be supplemented with *vitamin D* at a dose of 800 IU per day to ensure a replete vitamin D status. Advice on an *adequate calcium intake* of 1000 mg per day from nutritional sources is considered a basic strategy in combination with osteoporotic drug treatment. If calcium intake to a target range of 1000 mg cannot be achieved through nutritional sources alone, a calcium supplement of 300 to 500 mg/day is recommended.

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